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Invited review

The pathology and pathophysiology of vascular dementia

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ABSTRACT

Vascular dementia (VaD) is widely recognised as the second most common type of dementia. Consensus and accurate diagnosis of clinically suspected VaD relies on wide-ranging clinical, neuropsychological and neuroimaging measures in life but more importantly pathological confirmation. Factors defining subtypes of VaD include the nature and extent of vascular pathologies, degree of involvement of extra and intracranial vessels and the anatomical location of tissue changes as well as time after the initial vascular event. Atherosclerotic and cardioembolic diseases combined appear the most common subtypes of vascular brain injury. In recent years, cerebral small vessel disease (SVD) has gained prominence worldwide as an important substrate of cognitive impairment. SVD is characterised by arteriolosclerosis, lacunar infarcts and cortical and subcortical microinfarcts and diffuse white matter changes, which involve myelin loss and axonal abnormalities. Global brain atrophy and focal degeneration of the cerebrum including medial temporal lobe atrophy are also features of VaD similar to Alzheimer's disease. Hereditary arteriopathies have provided insights into the mechanisms of dementia particularly how arteriolosclerosis, a major contributor of SVD promotes cognitive impairment. Recently developed and validated neuropathology guidelines indicated that the best predictors of vascular cognitive impairment were small or lacunar infarcts, microinfarcts, perivascular space dilation, myelin loss, arteriolosclerosis and leptomeningeal cerebral amyloid angiopathy. While these substrates do not suggest high specificity, VaD is likely defined by key neuronal and dendro-synaptic changes resulting in executive dysfunction and related cognitive deficits. Greater understanding of the molecular pathology is needed to clearly define microvascular disease and vascular substrates of dementia.

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1. Introduction

Worldwide cerebrovascular disease (CVD) is likely the most common cause of cognitive impairment even above Alzheimer's disease (AD). The most prominent form of CVD is ischaemic strokes or cerebral ischaemic injury. Old age remains the strongest risk factor for strokes and other types of CVD. CVD involves arteriosclerotic changes in the cerebral or systemic vasculature, and often both, that likely begin during a considerable period prior to the manifestation of an overt stroke-like or CVD accident. While early or subtle changes may not necessarily be recognised clinically, they may be evident radiologically as white matter (WM) and silent lesions, mostly in form of lacunar infarcts. For example, 20% of healthy elderly people will bear magnetic resonance imaging (MRI)-defined silent brain infarcts and up to 50% of these are detected in selected patient cohorts (Vermeer et al., 2007). Hypertensive small-vessel disease (SVD) is thought to be the main risk factor for these infarcts, which may be associated with subtle deficits in physical and cognitive function that commonly go unnoticed, particularly in older age. In recent years, SVD has taken precedence as a radiological concept (Wardlaw et al., 2013) and refers to an intracranial disorder which involves pathological changes within and at the surfaces of brain microvessels including perforating arteries and arterioles, capillaries and venules. SVD comprises tissue injury in both the cortical and subcortical grey and white matter. However, SVD often coexists with atherosclerosis involving large extracranial vessels and cardioembolic (CE) disease (Li et al., 2015).

Vascular dementia (VaD) is widely regarded as the second most common type of dementia. VaD may culminate from global or focal effects of vascular disease. It is also characterised as a neurocognitive disorder, which also incorporates behavioural symptoms, locomotor abnormalities e.g. Parkinsonian-like gait disorder, dysarthria and autonomic dysfunction. The relatively recently described umbrella term vascular cognitive impairment (VCI) encompasses all causes of CVD including hereditary forms that lead to early and severe forms of dementia syndromes (Table 1). Within the spectrum of CVD and VaD, the most common vascular contributor to dementia is cerebral SVD (Wardlaw et al., 2013). As the older population survives longer (Corraini et al., 2017; Sacco and Dong, 2014), VaD more often than not will involve the SVD syndrome (Fig. 1).

In this review, I mostly focus on cerebral SVD but also provide recent updates on the understanding of key vascular lesions and tissue changes, which contribute to dementia. It is clear that despite the strong and unambiguous evidence that vascular factors and vascular disease contribute to the global burden of brain disease, dementia prognosis and research has mostly focused on AD. Vascular causes of dementia and their contribution to neurodegenerative processes have not been widely emphasised. The recognition of subtypes of clinical VaD (Table 1) was an important step forward towards current pathological classification based on vascular aetiology. It was subsequently recognised that multi-infarct dementia (MID) predominantly results from multiple large cortical infarcts attributed to large vessel disease whereas dementia associated with subcortical ischemic lesions or Binswanger's disease involving subcortical structures and the WM results from changes in intracranial small vessels. The older term Binswanger's disease is equated with SVD in which hypertensive disease is prominent (Rosenberg, 2017).

1.1. Definitions of vascular cognitive impairment, vascular cognitive disorder and VaD

The concept of VCI has been in use for more than 2 decades but it came into existence to empower an unique label for all conditions of vascular origin or impaired brain perfusion VCI (Gorelick et al., 2011; Hachinski et al., 2006a; O'Brien et al., 2003). While useful, it continually challenges how degrees of pathological changes correlate with the degree of impaired cognition in the continuum of VCI. The description vascular cognitive disorder (Sachdev, 1999) also incorporates a continuum comprising cognitive disorders of vascular aetiology with diverse pathologies and clinical manifestations. Therefore, in the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM) or DSM-V criteria and guidelines, categories of mild and major vascular cognitive disorders were introduced (Association, 2013). Vascular cognitive disorder indicates a global diagnostic category, restricting the term VCI to patients whose cognitive impairment fell short of dementia (Roman, 2002). The major neurocognitive disorder classification, meant to describe frank dementia as a substitute for VaD appears to fit better with patients, and more adapted to neurodegenerative cognitive disorders for which memory impairment is not predominant but comprises substantial frontal lobe pathology (Sachdev et al., 2014). More recently, refinement towards a standardised diagnosis of VCI was attained in a Delphi analysis undertaken by a large group of clinicians and researchers (Skrobot et al., 2017a, 2017b). This analysis conducted over six survey rounds by the vascular impairment of cognition classification consensus study (VICCCS) agreed to guidelines for the diagnosis of 'Mild' and 'Major' forms of VCI. The use of 'Mild' and 'Major' subdivisions of the severity of impairment aligns with the revised terminology in DSM-5. VICCCS also agreed that the Major forms of VCI or VaD should be classified into four main subtypes including subcortical ischaemic vascular dementia or SIVaD, MID or cortical dementia, post-stroke dementia (PSD) and mixed dementias, which could be subdivided according to respective neurodegenerative pathologies. VICCCS participants further endorsed the National Institute of Neurological Disorders-Canadian Stroke Network neuropsychological assessment protocols and recommendations for imaging (Skrobot et al., 2017b). Cognitive impairment or dementia following stroke is relatively common (Leys et al., 2005; Mok et al., 2017; Pendlebury and Rothwell, 2009). Incident dementia after stroke or PSD may develop within three months or after a stabilisation period of a year or longer after stroke injury (Allan et al., 2012; Bejot et al., 2011; Pohjasvaara et al., 1997). However, PSD can have a complex aetiology with varying combinations of large artery disease (LAD) and SVD as well as non-vascular pathology. Stroke injury or CVD may unmask other prexisting disease processes such as AD. We have recently demonstrated that at least 75% of PSD cases fulfilling relevant clinical guidelines for VCI (Hachinski et al., 2006b) are pathologically confirmed as VaD with little mostly age-related AD pathology (Allan et al., 2012). Moreover, the presence of any age-related hippocampal AD lesions did not differentiate demented from non-demented post-stroke subjects (Akinyemi et al., 2017).

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